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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 January 2000 (04.01.00)	
International application No. PCT/NO99/00141	**Applicant's or agent's file reference** P9828
International filing date (day/month/year) 30 April 1999 (30.04.99)	**Priority date** (day/month/year) 08 May 1998 (08.05.98)
Applicant GAUDERNACK, Gustav et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 December 1999 (02.12.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PCT/NO99/00143
P9802 PCT

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

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NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

LILLEGRAVEN, Rita
Norsk Hydro ASA
N-0240 Oslo
NORVÈGE

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
23 September 1999 (23.09.99)	
Applicant's or agent's file reference	**International application No.**
P9802	PCT/NO99/00143

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

NORSK HYDRO ASA (for all designated States except US)
GAUDERNACK, Gustav et al (for US)

International filing date	:	03 May 1999 (03.05.99)
Priority date(s) claimed	:	08 May 1998 (08.05.98)
Date of receipt of the record copy by the International Bureau	:	16 September 1999 (16.09.99)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,SD,SL,SZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
National :AE,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CU,CZ,DE,DK,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,PL,PT,RO,RU,SD.SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,US,UZ,VN,YU,ZA,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase
- [ ] confirmation of precautionary designations
- [ ] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

Marie-José Devillard

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

REC'D 22 AUG 2000

WIPO PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

15

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P9828		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NO99/00141	30/04/1999	08/05/1998
International Patent Classification (IPC) or national classification and IPC C07K14/435		
Applicant NORSK HYDRO ASA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/12/1999	17.08.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Strobel, A Telephone No. +49 89 2399 7362

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NO99/00141

I. Basis of th r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-20	as originally filed

Claims, No.:

1-25	as received on	25/05/2000	with letter of	22/05/2000

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	11
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV

Lack of unity of invention

The claims, inasmuch as they relate to Alzheimer's disease or to Down's syndrome, are not united by a common inventive concept. In view of the numerous objections raised under V. and VIII., the examiner did not pursue, at this stage, a unity objection. However, such an objection may be raised later during the national phase.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 9712992 A2

D2: FRED W. VAN LEEUWEN ET AL: "Frameshift Mutants of Beta Amyloid Precursor Protein and Ubiquitin-B in Alzheimer's and Down Patients", SCIENCE, USA, 09. January 1998, vol. 279, no. , pages 242 to 247

D3: WO9532731 A2

1. The application concerns the use of peptides derived from mutant ßAPP and Ubiquitin B proteins for the treatment of the neurodegenerative diseases, Alzheimer's Disease (AD) and Down's Syndrome (DS). These peptides origin from ßAPP or Ubi-B proteins containing nonsense amino acids due to frameshift mutations of the corresponding gene or mRNA transcript. Since peptides derived at least partially from the mutated sequence stretches of ßAPP or Ubi-B are new and "non-self" to the organism, it should be possible to raise a T cell response against these peptides after immunization of individuals suffering from AD or DS or at risk of developing these diseases, thereby specifically destroying the cells of the nervous system displaying the ßAPP or Ubi-B mutations associated with AD or DS.

   D1 reveals methods and reagents for diagnosis and treatment of AD and DS. In particular, D1 provides methods and reagents for analysing the presence of frameshift mutations of ßAPP and Ubi-B associated with AD and DS.

   D2 discloses the frameshift mutations of the ßAPP and Ubi-B proteins and reports on their association with AD and DS. These are the mutations on which the application is based.

D3 concerns the treatment of certain cancers which are associated with frameshift mutations in proteins. D3 describes peptide fragments of these mutated proteins that encompass mutated amino acids and their use for therapy. These peptides elicit a T cellular immune response. D3 claims also cDNA sequences coding for these peptides.

2. The underlying problem of the invention is to provide therapeutic approaches for the treatment of the neurodegenerative diseases, AD and DS. This problem is solved by the use of peptides for triggering a cellular immune response involving T cells. The peptides are derived from regions of two frameshift-mutated proteins associated with the diseases.
D3 reveals exactly the same solution for the treatment of certain cancers: D3 states that frameshift-mutated proteins associated with disease are "new" to the organism and can therefore be used for immunologic treatment of these diseases (e.g., page 3, lines 23-27). This anticipates the central presumption of the application, as stated on page 3, lines 13-16. D3 characterizes said peptides thoroughly as immunogenic (e.g., figures 1-5).
Moreover, D1 describes methods of identifying mutated regions in frameshift-mutated proteins in neurodegenerative diseases such as AD and DS. The teaching of D1 and D3 makes it obvious to the skilled person that the methods of D3 can readily be applied to AD and DS by using the detection methods of D1.
The fact that D1 concerns somatic mutations does not constitute a limitation of D1. In fact, the mutations which form the basis of the peptides of the alleged invention are also somatic mutations, even if they are mutations at the transcriptional level. Furthermore, the subject-matter of the whole set of claims is not at all defined by the precise mechanism of the underlying mutation. The whole set of claims is only defined by the technical feature "frameshift mutation", be it at the gene or transcriptional level.

The examiner cannot agree with the opinion expressed by the applicants that the man skilled in the art would not combine D1 with D3 for the following reasons:
First, in order for the man skilled in the art to combine the teachings of prior art documents, it is not necessary that said prior art documents refer one to another. In fact, if this were the case, then the problem of inventive step would incorrectly be mutated into a problem of novelty. If the authors of D1 or D2 had referred explicitly

to D3, then the whole set of claims of the application would be considered as not novel.

Furthermore, D3 states several times that the approach disclosed therein can be applied in general to diseases that are associated with frameshift mutations, and not only to cancers (page 1, lines 18-23; page 3, line 8-page 4, line 26). Inversely, D1 discloses in its introduction the association of cancers with somatic mutations (page 1, lines 18-27) and is aimed at identifying, detecting and treating of cancers and neurodegenerative diseases such as AD and DS (page 2, lines 21-25). D1 further states that frameshift mutations may in general be correlated with disease (page 5, lines 4-7). This means that it would be obvious to the man skilled in the art seeking to find therapeutic approaches for the treatment of AD and DS to combine D1 with D3.

Thus, the solution of the technical problem of the invention is not inventive and claims 1-10 do not satisfy Article 33(3) PCT (a variation of the length (see claims 6-9) can certainly not establish an inventive step).

3. The additional features of the present claims 11-25 are either trivial or conventional in the art or within the competence of a skilled man seeking to improve the prior art processes mentioned in the search report and in the present opinion, so that the subject-matter of said claims also lacks an inventive step **(Article 33(3) PCT).**

4. For the assessment of the present claims 1-10, and 12-25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

1. Claims 1-10, and 18-25 concern peptides or DNAs coding for peptides that elicit a T cell response. These claims lack experimental support, since there are no data at all showing by in vitro or in vivo studies that claimed peptides activate T cells (extensive experiments addressing this point are presented in D3).
Therefore, claims 1-10, and claims 18-25 lack support by the description (Article 6 PCT).

2. Claim 1 concerns a peptide which is a "fragment of a mutant ßAPP or Ubi-B protein arising from a frameshift mutation associated with Alzheimer's disease or Down syndrome".
The amino acid sequence of the mutated ßAPP and Ubi-B proteins are not deducible from the wording of claim 1 (there is no SEQ ID specifying the sequence of said mutated proteins). This means that it is not possible for a skilled person neither to determine the sequence of the claimed peptides nor to conceive DNA sequences that could encode the claimed peptides.
Finally, it is not specified what is stimulated in claims 16, 17, 21, and 25.
Thus, claims 1-9, and 11-25 are unclear and do not satisfy the requirements of Article 6 PCT.

3. The objection concerning "and/or" (paragraph VIII.2. of Written Opinion) has not been addressed by the applicant for claim 14: it is not clear what the alternative and/or in said claim could mean. ßAPP and Ubi-B are completely different proteins so that it seems impossible that a common peptide could be derived from both proteins (that is exactly implied by the alternative "and").

PATENT COOPERATION TREA

P9828 PCT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

LILLEGRAVEN, Rita
Norsk Hydro ASA
N-0240 Oslo
NORVEGE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 17. 08. 00
Applicant's or agent's file reference P9828	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NO99/00141	30/04/1999	08/05/1998

Applicant
NORSK HYDRO ASA et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Vullo, C Tel.+49 89 2399-8061

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P9828		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NO99/00141	30/04/1999	08/05/1998
International Patent Classification (IPC) or national classification and IPC C07K14/435		
Applicant NORSK HYDRO ASA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

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3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/12/1999	17.08.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Strobel, A Telephone No. +49 89 2399 7362

Form PCT/IPEA/409 (cover sheet) (January 1994)

CLAIMS

1. A peptide for use in treatment of Alzheimer's disease or Down's syndrome, said peptide characterised in that it:

a) is a fragment of a mutant βAPP or Ubi-B protein arising from a frameshift mutation associated with Alzheimer's disease or Down syndrome;

and

b) consists of at least one amino acid of the mutant part of the mutant βAPP or Ubi-B protein;

and

c) comprises 0-10 amino acids corresponding to the carboxyl terminus of the normal part of the protein sequence preceding the amino terminus of the mutant sequence and may further extend to the carboxyl terminus of the mutant part of the protein as determined by a new stop codon generated by the relevant frameshift mutation;

wherein the total number of amino acids from (b) and (c) is at least 8;

and

d) induces, either in its full length or after processing by antigen presenting cells, T cell responses.

2. A peptide according to claim 1 characterised in that it contain 8-25 amino acids.

3. A peptlde according to claim 1 characterised in that it contain 9-20 amino acids.

4. A peptide according to claim 1 characterised in that it contain 9-16 amino acids.

5. A peptide according to claim 1 characterised in that it 5 contain 8-12 amino acids.

6. A peptide according to claim 1 characterised in that it contain 20-25 amino acids.

7. A peptide according to claim 1 characterised in that it contains 9 amino acids.

8. A peptide according to claim 1 characterised in that it contains 12 amino acids.

9. A peptide according to claim 1 characterised in that it contains 13 amino acids.

10. A peptide according to claim 1 characterised in that it is selected from a group of peptides having the following sequence identity numbers: SEQ ID NO: 1 - SEQ ID NO: 10 or a fragment of any of these.

11. A pharmaceutical composition comprising a peptide according to any of the above claims and a pharmaceutically acceptable carrier or diluent.

12. A vaccine for Alzheimer's disease comprising a peptide according to any of the claims 1-10 and a pharmaceutically acceptable carrier or diluent.

13. Use of a peptide according to any of the claims 1-10 for the preparation of a pharmaceutical composition for treatment or prophylaxis of Alzheimer's disease or treatment of Down syndrome.

14. Method for vaccination of a person disposed for or afflicted with Alzheimer's disease, consisting of administering at least one peptide according to the claims 1-10, one or

more times, in an amount sufficient for induction of specific T-cell immunity to mutant βAPP and/or mutant Ubi-B peptides associated with Alzheimer's disease and/or Down syndrome.

15. Method according to claim 14 wherein the amount of the peptides is in the range of 1 microgram (1 μg) to 1 gram (lg) and preferentially in the rage of 1 microgram (1 μg) to 1 milligram (1 mg) for each administration.

16. Method for treatment of a patient afflicted with Alzheimer's disease or Down syndrome, by stimulating *in vivo* or *ex vivo* with peptides according to the claims 1-10.

17. Method according to claim 16 wherein the amount of the peptides used is in the range of 1 microgram (1 μg) to 1 gram (lg) and preferentially in the rage of 1 microgram (1 μg) to 1 milligram (1 mg) for each administration.

18. An isolated DNA sequence for use in treatment of Alzheimer's disease or Down's syndrome comprising a DNA sequence or variants thereof encoding a frameshift mutant peptide according to claim 1.

19. An isolated DNA sequence according to claim 18 encoding peptides comprising seq. id. no: 1-10 or variants thereof.

20. Use of a DNA sequence according to any of the claims 19-20 for the preparation of a pharmaceutical composition for treatment or prophylaxis of Alzheimer's disease or treatment of Down syndrome.

21. Method for treatment of a person disposed for or afflicted with Alzheimer's disease or afflicted with Down syndrome, by stimulating *in vivo* or *ex vivo* with DNA sequences according to the claims 18-19.

22. A plasmid or virus vector comprising DNA sequences of claim 17 encoding a frameshift mutant βAPP peptide and/or Ubi-B peptide associated with Alzheimer's disease or Down syndrome.

23. A vector according to claim 22 wherein the vector is *E. coli* plasmid, a Listeria vector and recombinant viral vectors. Recombinant viral vectors include, but are not limited to orthopox virus, canary virus, capripox virus, suipox virus, vaccinia, baculovirus, human adenovirus, SV40 or bovine papilloma virus.

24. Use of a plasmid or virus vector according to claim 22 for the preparation of a pharmaceutical composition for treatment or prophylaxis of Alzheimer's disease or treatment of Down syndrome.

25. Method for treatment of a person disposed for or afflicted with Alzheimer's disease or afflicted with Down syndrome, by stimulating *in vivo* or *ex vivo* with plasmids or virus vectors according to claim 22.